

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number : 040109**

**Trade Name: ACETAMINOPHEN, CAFFINE AND  
DIHYDROCODEINE BITARTRATE CAPSULES  
356.4MG/30MG/16MG**

**Generic Name: Acetaminophen, Caffeine and  
Dihydrocodeine Bitartrate Capsules 356.4mg/30mg/16mg**

**Sponsor : Mikart, Inc.**

**Approval Date: August 26, 1997**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 040109**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number    040109**

**APPROVAL LETTER**

Mikart, Inc.  
Attention: Cerie B. McDonald  
1750 Chattahoochee Ave., N.W.  
Atlanta, GA 30318-2112

AUG 26 1997

|||||

Dear Madam:

i This is in reference to your abbreviated new drug application dated July 18, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg/30 mg/16 mg.

Reference is also made to your amendments dated January 12, 1995, June 30 1997, and July 18, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, 356.4 mg, 30 mg, and 16 mg, respectively, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (DHC plus® Capsules of the Purdue Frederick Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

8/26/97

Douglas L. Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 040109**

**FINAL PRINTED LABELING**

Exp. Date:  
Lot No.:  
USUAL DOSAGE: See package insert for full prescribing information.  
WARNING: Keep this and all medications out of the reach of children.

NDC 46672-267-24



ACETAMINOPHEN  
CAFFEINE  
AND  
DIHYDROCODEINE BITARTRATE\*  
CAPSULES

356.4 mg  
30 mg  
16 mg

(\*WARNING: May be habit-forming)  
CAUTION: Federal law prohibits dispensing without prescription.

Contents: 4 Capsules  
Manufactured by:  
MIKART, INC.  
Atlanta, GA 30318

PHYSICIAN'S SAMPLE

Store at controlled room temperature  
15°-30°C (59°-86°F). Protect from moisture.

Rev. 12/95

Code 672A24

Exp. Date:  
Lot No.:  
USUAL DOSAGE: See package insert for full prescribing information.  
WARNING: Keep this and all medications out of the reach of children.

NDC 46672-267-10



ACETAMINOPHEN, CAFFEINE, AND  
DIHYDROCODEINE BITARTRATE\* CAPSULES  
356.4 mg/30 mg/16 mg

Each capsule contains:  
Acetaminophen . . . . . 356.4 mg  
Caffeine . . . . . 30 mg  
Dihydrocodeine Bitartrate\* . . . . . 16 mg  
(\*WARNING: May be habit-forming.)

CAUTION: Federal law prohibits dispensing without prescription.

Contents: 100 Capsules  
Manufactured by:  
MIKART, INC.  
Atlanta, GA 30318

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.  
Store at controlled room temperature  
15°-30°C (59°-86°F). Protect from moisture.

Rev. 12/95

Code 672A10

# ACETAMINOPHEN, CAFFEINE AND DIHYDROCODEINE BITARTRATE\* CAPSULES III

356.4 MG/30 MG/16 MG

## DESCRIPTION:

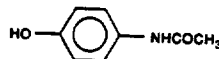
Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules are supplied in capsule form for oral administration.

Each red capsule contains:

|                                  |          |
|----------------------------------|----------|
| Acetaminophen .....              | 356.4 mg |
| Caffeine .....                   | 30 mg    |
| Dihydrocodeine Bitartrate* ..... | 16 mg    |

(\*Warning: May be habit forming.)

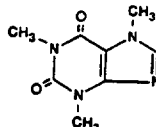
Acetaminophen (4'-hydroxyacetanilide), a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$

M.W. 151.17

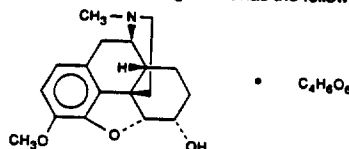
Caffeine (1,3,7-trimethylxanthine), a bitter, white crystalline powder, is a central nervous system stimulant. It has the following structural formula:



$C_8H_{10}N_4O_2$  (anhydrous)

M.W. 194.19

Dihydrocodeine Bitartrate (4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol (+)-tartrate), an odorless, fine white powder is an opioid analgesic. It has the following structural formula:



$C_{19}H_{23}NO_5 \cdot C_4H_6O_6$

M.W. 451.48

In addition each capsule also contains the following inactive ingredients: alginic acid, microcrystalline cellulose, stearic acid. The capsule is composed of: FD&C Blue #1, FD&C Red #40, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. Imprinting ink composed of: ammonium hydroxide, isopropyl alcohol, n-butyl alcohol, pharmaceutical glaze (modified) in SD-45, propylene glycol, simethicone, and titanium dioxide.

## CLINICAL PHARMACOLOGY:

Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules contain dihydrocodeine which is a semi-synthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to those of codeine; the most prominent of these involve the central nervous system and organs with smooth muscle components. The principal action of therapeutic value is analgesia.

This combination product also contains acetaminophen, a non-opiate, non-salicylate analgesic and antipyretic.

This combination product contains caffeine as an analgesic adjuvant. Caffeine is also a CNS and cardiovascular stimulant.

## INDICATIONS AND USAGE:

Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS:

This combination product is contraindicated in persons with hypersensitivity to dihydrocodeine, codeine, acetaminophen, caffeine, or the other components noted above.

## WARNINGS:

Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

## PRECAUTIONS:

**General:** Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules should be given with caution to certain patients such as the elderly or debilitated.

Acetaminophen is relatively non-toxic at therapeutic doses, but should be used with caution in patients with severe renal or hepatic disease.

Caffeine in high doses may produce CNS and cardiovascular stimulation and GI irritation.

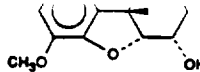
**Information for Patients:** Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules should be cautioned accordingly.

## Drug Interactions:

### Dihydrocodeine

Patients receiving other narcotic analgesics, general anesthetics, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

### Caffeine



2

$C_{18}H_{23}NO_7 \cdot C_4H_5O_6$

M.W. 451.48

In addition each capsule also contains the following inactive ingredients: alginic acid, micro-crystalline cellulose, stearic acid. The capsule is composed of: FD&C Blue #1, FD&C Red #40, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. Imprinting ink composed of: ammonium hydroxide, isopropyl alcohol, n-butyl alcohol, pharmaceutical glaze (modified) in SD-45, propylene glycol, simethicone, and titanium dioxide.

#### CLINICAL PHARMACOLOGY:

Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules contain dihydrocodeine which is a semi-synthetic narcotic analgesic related to codeine, with multiple actions qualitatively similar to those of codeine; the most prominent of these involve the central nervous system and organs with smooth muscle components. The principal action of therapeutic value is analgesia.

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This combination product contains caffeine as an analgesic adjuvant. Caffeine is also a CNS and cardiovascular stimulant.

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This combination product is contraindicated in persons with hypersensitivity to dihydrocodeine, codeine, acetaminophen, caffeine, or the other components noted above.

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#### PRECAUTIONS:

**General:** Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules should be given with caution to certain patients such as the elderly or debilitated.

Acetaminophen is relatively non-toxic at therapeutic doses, but should be used with caution in patients with severe renal or hepatic disease.

Caffeine in high doses may produce CNS and cardiovascular stimulation and GI irritation.

**Information for Patients:** Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules should be cautioned accordingly.

#### Drug Interactions:

##### Dihydrocodeine

Patients receiving other narcotic analgesics, general anesthetics, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

##### Caffeine

Caffeine may enhance the cardiac inotropic effects of beta-adrenergic stimulating agents. Co-administration of caffeine and disulfiram may lead to a substantial decrease in caffeine clearance. Caffeine may increase the metabolism of other drugs such as phenobarbital and aspirin. Caffeine accumulation may occur when products or foods containing caffeine are consumed concomitantly with quinolones such as ciprofloxacin.

**Pregnancy: Teratogenic Effects — Pregnancy Category C.** Animal reproduction studies have not been conducted with Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules. It is also not known whether this product can cause fetal harm when administered to

pregnant women or can affect reproduction capacity in males and females. This product should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from this product, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Since there is no experience in pediatric patients who have received this drug, safety and efficacy in pediatric patients have not been established.

#### **ADVERSE REACTIONS:**

The most frequently observed reactions include light-headedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, and skin reactions.

#### **DRUG ABUSE AND DEPENDENCE:**

This combination product is subject to the provisions of the Controlled Substance Act, and has been placed in Schedule III.

Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

Prolonged, high intake of caffeine may produce tolerance and habituation. Physical signs of withdrawal, such as headaches, irritation, nervousness, anxiety, and dizziness may occur upon abrupt discontinuation.

#### **OVERDOSAGE:**

Following an acute overdosage with Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, toxicity may result from the dihydrocodeine, acetaminophen, or, less likely, caffeine component. An overdose is a potentially lethal polydrug overdose situation, and consultation with a regional poison control center is recommended. A listing of the poison control centers can be found in standard references such as the *Physician's Desk Reference*.

**Signs and Symptoms and Laboratory Findings:** Toxicity from dihydrocodeine is typical of opiates and includes pinpoint pupils, respiratory depression, and loss of consciousness. Convulsions, cardiovascular collapse, and death may occur. With acetaminophen, dose-dependent hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, thrombocytopenia may occur. Early symptoms of hepatotoxicity include nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams or fatalities with less than 15 grams. Acute caffeine poisoning may cause insomnia, restlessness, tremor, delirium, tachycardia, extrasystoles, and seizures.

Because overdose information on this combination product is limited, it is unclear which of the signs and symptoms of toxicity would manifest in any particular overdose situation.

#### **Treatment**

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced with syrup of ipecac, if the patient is alert and has adequate laryngeal reflexes. Oral activated charcoal should follow. The first dose should be accompanied by an appropriate cathartic. Gastric lavage may be necessary. Hypotension is usually hypovolemic and should be treated with fluids. Endotracheal intubation and artificial respiration may be necessary. Peritoneal or hemodialysis may be necessary. If hypoprothrombinemia occurs, Vitamin K should be administered.

The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone hydrochloride (usually 0.4 to 2.0 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Re-administration may be necessary. Naloxone should not be given in the absence of clinically significant respiratory or circulatory depression secondary to opioid overdose.

In adults and adolescents, regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time since ingestion. Do not await the plasma concentration determination of acetaminophen before administering acetylcysteine. Serum liver enzyme levels should be quantitated. Therapy in children involves a similar treatment scheme; however, a regional Poison Control Center should be contacted.

No specific antidote is available for caffeine. In addition to the supportive measures above, administration of demulcents such as aluminum hydroxide gel may diminish GI irritation. Seizures may be treated with intravenous diazepam or a barbiturate.

#### **DOSAGE AND ADMINISTRATION:**

The usual adult dosage is two (2) Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules orally every four (4) hours. Dosage should be adjusted according to the severity of the pain and the response of the patient. No more than twelve (12) capsules should be taken in a 24-hour period.

#### **HOW SUPPLIED:**

Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules, containing acetaminophen 356.4 mg, caffeine 30 mg and dihydrocodeine bitartrate 16 mg ("Warning: May be habit forming"), are supplied in bottles of 100 capsules (NDC # 46672-267-10). Capsules are red, body and cap, and are imprinted with "PAL" on the cap and "2693" on the body in white ink.

Store at controlled room temperature, 15°C - 30°C (59°F - 86°F). Protect from moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

#### **CAUTION:**

Federal law prohibits dispensing without prescription.

Manufactured by:  
**MIKART, INC.**  
Atlanta, Georgia 30318

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER    040109**

**CHEMISTRY REVIEW(S)**

1. CHEMISTRY REVIEW NO. 4

2. ANDA 40-109

3. NAME AND ADDRESS OF APPLICANT

Mikart, Inc.  
2090 Marietta Boulevard  
Atlanta, GA 30318-2147

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies that, to the best of their knowledge, no patent information has been filed with the FDA and it is not entitled to a period of marketing exclusivity.

Innovator: Salvoy - DHC Plus, transfer of ownership of application to Purdue Frederick - Compal

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Acetaminophen, Caffeine  
Dihydrocodeine Bitartrate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm: 7/18/94 - Original  
1/12/95 - NC, Bio. response to phone memo.  
5/5/95 - Response to 1st def. letter (chem. & labeling.  
3/27/96 - Response to 2nd def. letter (chem. & labeling.  
4/15/96 - Response to phone memo, color and imprint.  
4/24/96 - Response to phone memo, imprint.  
6/30/97 - Response to 3rd def. letter (CGMP).  
Subject of this review.  
7/18/97 - Response to phone memo. Subject of this review.

FDA: 8/12/94 - Acknowledgment  
12/29/94 - 1st def. letter (chem. & labeling).  
2/7/95 - 1st. Bio. review.  
11/30/95 - 2nd def. letter (chem. & labeling).  
4/11/96 - Phone memo, information on color and imprint.  
4/22/96 - Phone memo, information on imprint.  
5/6/96 - Phone memo, listed drug product.  
7/12/96 - Phone memo, RLD listed by firm is correct.  
7/17/96 - 3rd def. letter (CGMP).  
7/17/97 - Phone memo, finished product specifications.

10. PHARMACOLOGICAL CATEGORY  
Narcotic analgesic

11. Rx or OTC  
R

12. RELATED IND/NDA/DMF(s)

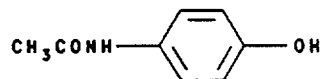
(b)4 - Confidential Business

13. DOSAGE FORM  
Capsule

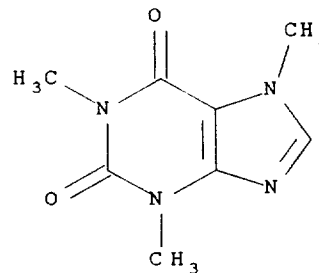
14. POTENCY  
356.4 mg/30 mg/16 mg

15. CHEMICAL NAME AND STRUCTURE

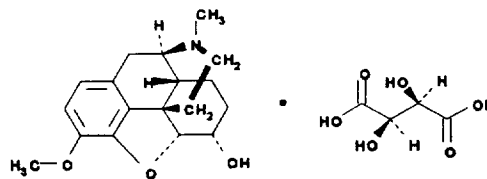
Acetaminophen USP  
 $C_8H_9NO_2$ ; M.W. = 151.16  
4'-Hydroxyacetanilide.  
CAS [103-90-2]



Caffeine USP  
 $C_8H_{10}N_4O_2$ ; M.W. = 194.19  
1,3,7-Trimethylxanthine.  
CAS [58-08-2]



Dihydrocodeine Bitartrate USP  
 $C_{18}H_{23}NO_3 \cdot C_4H_6O_6$ ; M.W. = 451.48  
4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6 $\alpha$ -ol(+)-tartrate (salt).  
CAS [125-28-0]  
(dihydrocodeine)



16. RECORDS AND REPORTS  
N/A

17. COMMENTS  
DMFs, EER, Method validation, and Bio. satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS  
Approval

19. REVIEWER:  
Norman Gregory

DATE COMPLETED:  
7/17/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040109

BIOEQUIVALENCE REVIEW(S)

FEB 7 1995

**Acetaminophen, Caffeine,  
and Dihydrocodeine Bitartrate**  
356.4 mg/30 mg/16 mg Capsules  
ANDA # 40-109  
Reviewer: Z.Z. Wahba  
wp# 40109wd.794

**Mikart, Inc.**  
Atlanta, GA  
Submission Date:  
July 18, 1994  
January 12, 1995

## Review of Dissolution Data and a Waiver Request

### I. BACKGROUND

The firm has submitted comparative in vitro dissolution data for its test drug product, Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules 356.4 mg/30 mg/16 mg, and the reference listed product, Solvay's DHC plus® Capsules, 356.4 mg/30 mg/16 mg, in support of a request for a waiver of in vivo bioequivalence requirements.

### II. FORMULATION COMPOSITION

The reference listed product contains the following active and inactive ingredients: acetaminophen, caffeine anhydrous, dihydrocodeine bitartrate, croscarmellose sodium, FD&C blue No. 1, FD&C green No. 3, gelatin, silica gel, silicon dioxide, sodium lauryl sulfate, corn starch, titanium dioxide and zinc stearate. The test product formulation is provided in the submission on page #96, vol. #1.1

#### Active Ingredients

Acetaminophen USP (Powder)  
Caffeine USP Anhydrous (Powder)  
Dihydrocodeine Bitartrate USP

#### Quantity/Capsule

356.40 mg  
30.00 mg  
16.00 mg

#### Inactive Ingredients

Microcrystalline Cellulose NF  
Alginate Acid NF  
Stearic Acid NF (Powder)

■(b)4-■  
Confidential

Capsule Weight

530.00 mg

Capsule Information

(b)4 - Confidential Business

(b)4 - Confidential Business

**III. DISSOLUTION**

The firm has submitted dissolution data for the test and reference products applying the following conditions:

Method: USP XXII apparatus I (Basket) at 100 rpm  
Medium: 900 ml water  
Temperature:  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$   
Number of Tablets: 12  
Specification: NLT (b)4(Q) is dissolved in 45 minutes  
Reference product: Solvay's DHC plus<sup>®</sup> Capsules, 356.4 mg/30 mg/16 mg (Lot #50969), expiration date 5/95.

**Table 1. In Vitro Dissolution Testing**

Drug (Generic Name): Acetaminophen, Caffeine and Dihydrocodeine Bitartrate  
Dose Strength: 356.4 mg/30 mg/16 mg  
ANDA No.: 40-109  
Firm: Mikart, Inc.  
Submission Date: July 18, 1994  
File Name: 40109wd.794

**I. Conditions for Dissolution Testing:**

USP XXII Basket: X      Paddle:      RPM: 100  
No. Units Tested: 12  
Medium: water      Volume: 900 mL  
Specifications: NLT/(b)(4)(Q) is dissolved in 45 minutes  
Reference Drug: Solvay's DHC plus®  
Assay Methodology: (b)(4)

**II. Results of In Vitro Dissolution Testing:**

| Sampling Times (Minutes) | Test Product Acetaminophen<br>Lot #K93839/940094A<br>Strength(mg) 356.4 |              |     | Reference Product Acetaminophen<br>Lot # 50969<br>Strength(mg) 356.4 |              |     |
|--------------------------|---|--------------|-----|--|--------------|-----|
|                          | Mean %  | Range        | %CV | Mean %   | Range        | %CV |
| 15                       | 97.9  | (b)(4) -     | 3.8 | 94.7   | (b)(4) -     | 3.7 |
| 30                       | 98.9  | Confidential | 3.6 | 97.2   | Confidential | 2.7 |
| 45                       | 99.0  | Business     | 3.4 | 97.4   | Business     | 2.6 |
| 60                       | 98.7  |              | 3.8 | 98.4   |              | 2.5 |

| Sampling Times (Minutes) | Test Product Caffeine<br>Lot #K93839/940094A<br>Strength(mg) 30 |              |     | Reference Product Caffeine<br>Lot #50969<br>Strength(mg) 30 |              |     |
|--------------------------|---|--------------|-----|---|--------------|-----|
|                          | Mean %  | Range        | %CV | Mean %  | Range        | %CV |
| 15                       | 102.9   | (b)(4) -     | 5.4 | 106.1   | (b)(4) -     | 3.6 |
| 30                       | 103.5   | Confidential | 5.0 | 106.4   | Confidential | 3.8 |
| 45                       | 103.2   | Business     | 4.9 | 105.3   | Business     | 3.8 |
| 60                       | 102.9   |              | 5.1 | 105.8   |              | 3.8 |

| Sampling Times (Minutes) | Test Product Dihydrocodeine Bitartrate<br>Lot #K93839/940094A<br>Strength(mg) 16 |              |     | Reference Product Dihydrocodeine Bitartrate<br>Lot #50969<br>Strength(mg) 16 |              |     |
|--------------------------|--|--------------|-----|--|--------------|-----|
|                          | Mean %   | Range        | %CV | Mean %   | Range        | %CV |
| 15                       | 102.3  | (b)(4) -     | 4.1 | 101.9  | (b)(4) -     | 4.2 |
| 30                       | 104.1  | Confidential | 4.3 | 103.2  | Confidential | 3.7 |
| 45                       | 104.4  | Business     | 4.0 | 104.0  | Business     | 4.1 |

|    |       |        |     |       |        |     |
|----|-------|--------|-----|-------|--------|-----|
| 60 | 103.8 | (b)4 - | 4.3 | 103.0 | (b)4 - | 3.9 |
|----|-------|--------|-----|-------|--------|-----|

1. The firm has stated in the submission that the dissolution testing data were generated utilizing (b)4 dissolution method (see ANDA #40-109, Vol. #1.1, pages 79-88 and vol. #1.4, pages 1165-1492).

#### IV. ASSAY AND CONTENT UNIFORMITY

1. The test product assay and content uniformity information are provided in the submission (see ANDA #40109, vol. #1.4, Page #1177).

##### Acetaminophen

Assay mean = 101.1%

Content uniformity = 100.7% (CV=4.4%)

##### Caffeine

Assay mean = 101.8%

Content uniformity = 101.4% (CV=4.9%)

##### Dihydrocodeine Bitartrate

Assay mean = 100.1%

Content uniformity = 99.6% (CV=6.1%)

2. The reference product content uniformity information is provided in the submission (see AND #40109, supplement dated Jan. 12, 1995, Page #0003). The assay potency of the reference product was not given.

##### Acetaminophen

Content uniformity = 98.8% (C=3.0%)

##### Caffeine

Content uniformity = 95.5% (C=3.4%)

##### Dihydrocodeine Bitartrate

Content uniformity = 93.3% (C=3.9%)

#### V. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
2. The test drug product contains the same active ingredients in the same strength and dosage form as the currently approved listed reference product.
3. The test drug product contains no inactive ingredient(s) that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

4. The dissolution data for the test product is acceptable.
5. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(d)(4)(ii) of the Bioavailability/Bioequivalence Regulations.

#### VI. RECOMMENDATION

1. The Division of Bioequivalence agrees that the information submitted by Mikart, Inc. on its drug product, Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules 356.4 mg/30 mg/16 mg falls under 21 CFR section 320.22(d)(4)(ii) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the firm's test product, Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules 356.4 mg/30 mg/16 mg is deemed bioequivalent to the reference listed product, Solvay's DHC plus® Capsules, 356.4 mg/30 mg/16 mg.
2. The dissolution testing conducted by Mikart, Inc. on its drug product, Acetaminophen, Caffeine and Dihydrocodeine Bitartrate Capsules 356.4 mg/30 mg/16 mg is acceptable.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of H<sub>2</sub>O, at 37°C using Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Not less than 1/2 of the labeled amount of each drug in the tablet is dissolved in 45 minutes.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.  
Division of Bioequivalence  
Review Branch III

RD INITIALLED MPARK  
FT INITIALLED MPARK

/S/

Feb 7, 1995

cc: ANDA# 40-109, original, HFD-658 (UGD), HFD-604 (Hare),  
HFD-658 (Park, Wahba), Drug File  
ZZWahba/120294/13195/40109wd.794